

Charles M. Lizza  
William C. Baton  
Sarah A. Sullivan  
SAUL EWING LLP  
One Riverfront Plaza, Suite 1520  
Newark, NJ 07102  
(973) 286-6700  
clizza@saul.com

*Attorneys for Plaintiffs  
Alkermes, Inc. and  
Alkermes Pharma Ireland Limited*

**UNITED STATES DISTRICT COURT  
DISTRICT OF NEW JERSEY**

ALKERMES, INC. and ALKERMES  
PHARMA IRELAND LIMITED,

Plaintiffs,

v.

TEVA PHARMACEUTICALS USA, INC.,

Defendant.

Civil Action No. 20-12470 (MCA)(MAH)

(Filed Electronically)

**ALKERMES'S OPENING POST-TRIAL BRIEF**

**TABLE OF CONTENTS**

	<b>Page</b>
INTRODUCTION .....	1
BACKGROUND .....	5
I.    The '499 Patent .....	5
A.    Overview of the '499 Patent .....	5
B.    The Asserted Claims of the '499 Patent .....	6
C.    The Invention of Claim 1 is Limited to a Single Injection of a Long-Acting Formulation Containing the Specified Amount of Naltrexone .....	7
II.    Overview of the Prior Art Search for a Treatment of Alcohol and Opioid Dependence Using a Long-Acting Naltrexone Formulation as of 2004 .....	9
III.   Alkermes's Development and Dr. Ehrich's Theory That Made Vivitrol® Possible.....	14
ARGUMENT .....	16
I.    Teva Did Not Prove by Clear and Convincing Evidence that the Asserted Claims Would Have Been Obvious To a POSA at the Time of the Invention.....	16
A.    Teva Bears the Heavy Burden of Proving Obviousness by Clear and Convincing Evidence .....	16
B.    The Problem Facing a POSA in 2004 .....	17
C.    Teva Did Not Prove By Clear and Convincing Evidence That Claims 1 and 5 Would Have Been Obvious Over Comer, Nuwayser, and Leavitt.....	19
1.    Teva Failed to Prove that a POSA Would Have Been Motivated to Treat Opioid or Alcohol Dependence With a Single Injection of a Long-Acting Formulation Containing the Claimed Amount of Naltrexone that Achieves the Claimed Naltrexone Exposure .....	19
2.    Teva Failed to Prove By Clear and Convincing Evidence That the Claimed Naltrexone Exposure Was Inherent to the Dose of Naltrexone In a Long-Acting Formulation .....	24
3.    Teva Failed to Prove By Clear and Convincing Evidence that a POSA Would Have Had a Reasonable Expectation of Success of the Claimed Invention Based on the Combination of Comer, Nuwayser, and Leavitt .....	26
D.    Teva Did Not Prove by Clear and Convincing Evidence That Claim 13 Would Have Been Obvious Over Comer, Nuwayser, and Leavitt .....	29

**TABLE OF CONTENTS**  
**(continued)**

	<b>Page</b>
E.     Teva Did Not Prove by Clear and Convincing Evidence That Claim 10 Would Have Been Obvious Over Comer, Nuwayser, and Leavitt .....	30
F.     Teva Did Not Prove by Clear and Convincing Evidence That Claim 2 Would Have Been Obvious Over Comer, Nuwayser, and Leavitt .....	31
G.     Objective Indicia of Nonobviousness Reinforce That Teva Failed to Establish Obviousness of the Asserted Claims by Clear and Convincing Evidence .....	32
II.    Teva Did Not Prove By Clear and Convincing Evidence That the Comparative AUC Limitation Is Indefinite.....	36
III.   Teva Failed to Prove by Clear and Convincing Evidence That the Asserted Claims Lack Written Description .....	38
CONCLUSION AND REMEDY.....	40

**TABLE OF AUTHORITIES**

	<b>Page(s)</b>
<b>Cases</b>	
<i>Allergan, Inc. v. Sandoz Inc.</i> , 796 F.3d 1293 (Fed. Cir. 2015).....	23
<i>Amgen Inc. v. F. Hoffmann-La Roche, Ltd.</i> , 580 F.3d 1340 (Fed. Cir. 2009).....	27
<i>In re Cyclobenzaprine</i> , 676 F.3d 1063 (Fed. Cir. 2012).....	17, 34
<i>Eli Lilly &amp; Co. v. Actavis Elizabeth LLC</i> , 435 F. App'x 917 (Fed. Cir. 2011).....	19
<i>Endo Pharm. Solutions v. Custopharm Inc.</i> , 894 F.3d 1374 (Fed. Cir. 2018).....	24
<i>In re Gordon</i> , 733 F.2d 900 (Fed. Cir. 1984).....	29
<i>Graham v. John Deere Co.</i> , 383 U.S. 1 (1966).....	17
<i>Harari v. Lee</i> , 656 F.3d 1331 (Fed. Cir. 2011).....	8
<i>Insite Vision Inc. v. Sandoz, Inc.</i> , 783 F.3d 853 (Fed. Cir. 2015).....	27, 39
<i>Insituform Techs., Inc. v. Cat Contracting, Inc.</i> , 99 F.3d 1098 (Fed. Cir. 1996).....	8
<i>In re Kotzab</i> , 217 F.3d 1365 (Fed. Cir. 2000).....	17
<i>KSR Int'l Co. v. Teleflex Inc.</i> , 550 U.S. 398 (2007) .....	38
<i>Microsoft Corp. v. i4i Ltd. P'ship</i> , 564 U.S. 91 (2011).....	16
<i>Millennium Pharm., Inc. v. Sandoz Inc.</i> , 862 F.3d 1356 (Fed. Cir. 2017).....	24, 35
<i>Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH</i> , 139 F.3d 877 (Fed. Cir. 1998).....	35

**TABLE OF AUTHORITIES**  
**(continued)**

	<b>Page(s)</b>
<i>Nautilus, Inc. v. Biosig Instruments, Inc.</i> , 572 U.S. 898 (2014) .....	36
<i>Ortho-McNeil Pharm., Inc. v. Mylan Labs.</i> , 348 F. Supp. 2d 713 (N.D.W. Va. 2004) .....	35
<i>Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.</i> , 520 F.3d 1358 (Fed. Cir. 2008).....	36
<i>Otsuka Pharm. Co. v. Sandoz, Inc.</i> , 678 F.3d 1280 (Fed. Cir. 2012).....	17
<i>Phillips v. AWH Corp.</i> , 415 F.3d 1303 (Fed. Cir. 2005) ( <i>en banc</i> ).....	7, 8
<i>Power Integrations, Inc. v. Fairchild Semiconductor Int’l, Inc.</i> , 711 F.3d 1348 (Fed. Cir. 2013).....	32
<i>Presidio Components, Inc. v. Am. Tech. Ceramics Corp.</i> , 875 F.3d 1369 (Fed. Cir. 2017).....	36
<i>Procter &amp; Gamble Co. v. Teva Pharms. USA, Inc.</i> , 566 F.3d 989 (Fed. Cir. 2009).....	34
<i>Sonix Tech. Co. v. Publ’ns Int’l, Ltd.</i> , 844 F.3d 1370 (Fed. Cir. 2017).....	37
<i>TI Grp. Auto. Sys. (N. Am.), Inc. v. VDO N. Am., L.L.C.</i> , 375 F.3d 1126 (Fed. Cir. 2004).....	7
<i>Vanda Pharms., Inc. v. West-Ward Pharms. Int’l Ltd.</i> , 887 F.3d 1117 (Fed. Cir. 2018).....	40
<i>WBIP, LLC v. Kohler Co.</i> , 829 F.3d 1317 (Fed. Cir. 2016).....	33

**TABLE OF ABBREVIATIONS**

<b>Parties</b>	
Alkermes or Plaintiffs	Alkermes, Inc. and Alkermes Pharma Ireland Limited
Teva or Defendant	Teva Pharmaceuticals USA, Inc.
<b>Patent-in-Suit</b>	
'499 Patent	U.S. Patent No. 7,919,499, titled "Naltrexone Long Acting Formulations and Methods of Use," which issued on April 5, 2011, from Application No. 11/083,167 (PTX-1) (DTX-1)
'499 Patent Prosecution History	Patent Prosecution History of U.S. Patent No. 7,919,499 (DTX-002)
Asserted Claims	Claims 1, 2, 5, 10, and 13 of the '499 patent
Ehrich Declaration	Declaration Under 37 C.F.R. 1.132 of the inventor, Dr. Elliot Ehrich, filed March 17, 2005 (PTX-52) (PTX-179)
Patent-in-suit	The '499 Patent
<b>References</b>	
1995 SBIR Grant	1995 SBIR Grant (PTX-9)
Alim	Alim et al., <i>Tolerability Study of a Depot Form of Naltrexone Substance Abusers</i> , 153 NAT'L INST. ON DRUG ABUSE MONOGRAPH 253 (1995) (PTX-190) (DTX-124)
ALK21-003 Protocol	Protocol for Alkermes ALK21-003 Phase 3 Clinical Trial finalized on December 4, 2001 (PTX-235)
ALK21-003 Clinical Study Report	ALK21-003 Clinical Study Report (PTX-236)
Chiang 1984	Chiang et al., <i>Kinetics of a Naltrexone Sustained-Release Preparation</i> , 36 CLINICAL PHARMACOLOGY AND THERAPEUTICS 704 (1984) (PTX-187) (DTX-131)
Chiang 1985	Chiang et al., <i>Clinical Evaluation of a Naltrexone Sustained-Release Preparation</i> , 16 DRUG AND ALCOHOL DEPENDENCE 1 (1985) (PTX-188)

**TABLE OF ABBREVIATIONS**  
(continued)

Comer	Sandra D. Comer, et al., <i>Depot Naltrexone: Long-Lasting Antagonism of the Effects of Heroin in Humans</i> , 159 PSYCHOPHARMACOLOGY 351, 351-360 (2002) (PTX-18) (DTX-009)
Heishman	Heishman et al., <i>Safety and Pharmacokinetics of a New Formulation of Depot Naltrexone</i> , 141 NAT'L INST. ON DRUG ABUSE MONOGRAPH SERIES 82 (1994) (PTX-23) (DTX-216)
Kranzler	Henry R. Kranzler, <i>Sustained-Release Naltrexone for Alcoholism Treatment: A Preliminary Study</i> , 22(5) ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH 1074, 1074-1079 (1998) (PTX-25) (DTX-217)
Krystal	Krystal et al., <i>Naltrexone in the Treatment of Alcohol Dependence</i> , 345 N. ENGL. J. MED. 1734, 1734-1739 (2001) (PTX-26)
Leavitt	Stewart B. Leavitt, <i>Evidence for the Efficacy of Naltrexone in the Treatment of Alcohol Dependence (Alcoholism)</i> , ADDICTION TREATMENT FORUM 1, 1-10 (2002) (PTX-27) (DTX-133)
Nuwayser	E. Nuwayser, U.S. Patent No. 7,157,102, titled "Multi-Layered Microcapsules and Method of Preparing Same," (DTX-215)
Olsen	Olsen et al., <i>A Review of Parenteral Sustained-Release Naltrexone Systems</i> , 28 NAT'L INST. ON DRUG ABUSE MONOGRAPH SERIES 187, 187-193 (1981) (PTX-36) (DTX-140)
ReVia PDR	<i>Physician's Desk Reference (ReVia)</i> (Ronald Arky et al. Eds., 53rd Ed. 1999) (PTX-38) (DTX-136)
Remington	<i>Remington's Pharmaceutical Sciences</i> , Anthony R. DiSanto, Bioavailability and Bioequivalency Testing, Ch. 76 (1990) (PTX-76)
The '477 patent	U.S. Patent No. 5,792,477 (DTX-095)
Sullivan	Sullivan et al., <i>A Randomized Trial Comparing Extended-Release Injectable Suspension and Oral Naltrexone, Both Combined With Behavioral Therapy, for the Treatment of Opioid Use Disorder</i> , 176 AM. J. PSYCHIATRY 129, 129-137 (2019) (PTX-40)
Tice	Tice et al., U.S. Patent No. 6,306,425, titled "Injectable Naltrexone Microsphere Compositions and Their Use in Reducing Consumption of Heroin and Alcohol" (PTX-44) (PTX-191) (DTX-137)

**TABLE OF ABBREVIATIONS**  
(continued)

Wright	Wright et al., U.S. Patent No. 6,264,987, titled “Method for Preparing Microparticles Having a Selected Polymer Molecular Weight” (PTX-43)
Verebey	Verebey et al., <i>Narcotic Antagonists: Naltrexone Pharmacology and Sustained-Release Preparations</i> , NALTREXONE: RESEARCH MONOGRAPH 28, 147-158 (1980) (DTX-213)
Vivitrol® Label	Vivitrol® Label, revised Oct. 2010 (DTX-004), revised May 2020 (PTX-48), revised Mar. 2021 (DTX-166)
<b>Pleadings</b>	
COL	Plaintiffs’ Post-trial Proposed Conclusions of Law (Section __, <i>infra</i> )
PFOF	Plaintiffs’ Post-trial Proposed Findings of Fact (Sections __, <i>infra</i> )
SF	Stipulation of Facts (D.I. 165, Tab 3)
<b>Miscellaneous</b>	
AUC	Area under the curve
FDA	U.S. Food and Drug Administration
NIDA	National Institute on Drug Abuse
PK	Pharmacokinetic
PLGA	Poly(lactide-co-glycolide)
POSA	Person of ordinary skill in the art
PTAB	U.S. Patent Trial and Appeal Board
PTO	U.S. Patent and Trademark Office

## INTRODUCTION

This case arises from Teva's request to sell a generic copy of Alkermes's Vivitrol<sup>®</sup> treatment for alcohol and opioid dependence before the expiration of Alkermes's '499 Patent, which protects the invention of that important drug treatment. Teva has admitted that its proposed generic product infringes the Asserted Claims of the '499 Patent. Accordingly, the only issues for trial were Teva's affirmative defenses of patent invalidity — (1) obviousness based on the combination of three publications (Comer, Leavitt, and Nuwayser), (2) indefiniteness of one claim limitation, and, in the alternative, (3) lack of written description of one claim limitation. For each of these defenses, in view of the statutory presumption of patent validity, Teva bore the burden of proof under the strict clear and convincing evidence standard. As discussed below, Teva did not prove invalidity applying the proper legal tests for its defenses.

The invention of Claim 1 of the '499 Patent is a method of treating alcohol and opioid dependence. The method administers a single injection of a long-acting formulation containing about 310-480 mg of naltrexone in PLGA (a biodegradable polymer). The formulation achieves a total blood exposure ("AUC") about three times greater than that of 50 mg/day of oral naltrexone, which was the standard of care for naltrexone treatment at the time of the invention. These three components — *in combination* — (1) treating individuals in need of naltrexone, (2) administering a single injection of a long-acting formulation with the specified dose of naltrexone and PLGA, and (3) the long-acting formulation achieving naltrexone exposure about three times greater than oral naltrexone, must be considered as a whole when evaluating Teva's arguments.

As the evidence at trial showed, Teva failed to prove that the '499 Patent would have been obvious to an ordinarily skilled person as of the time of the invention in April 2004, without the benefit of hindsight knowledge of Alkermes's own work. As the evidence at trial established, as

early as 1981, the art had sought a long-acting naltrexone treatment that was safe and effective and would improve compliance compared to oral naltrexone. Actually developing such a treatment, however, was a challenging goal; what followed was a span of decades in which various researchers explored experimental long-acting naltrexone formulations, reporting problems in the studies that reflected the challenges in this area of addiction treatment. This prior art would not have clearly and convincingly led a POSA, who lacked hindsight knowledge of Alkermes's invention, toward a successful treatment compared to oral naltrexone.

The prior art as a whole leading up to the invention was focused on the opiate blockage that resulted from the approved 50 mg/day oral standard for a treatment using naltrexone. The inventor of the '499 Patent, Dr. Elliott Ehrich, explained at trial his conception of a different path based on a theory that brain dysregulation was the culprit for dependence disorders. He therefore favored a markedly higher total blood exposure of naltrexone compared to oral naltrexone — one of the three key components of the Asserted Claims, which is expressly identified in the Vivitrol<sup>®</sup> label (and in Teva's product label).

Teva did not cite prior art that taught Dr. Ehrich's theory to a POSA. Rather, Teva's expert, Dr. Westreich, *admitted* that he could not identify any prior art reference that discussed the pursuit of a treatment using a long-acting formulation of naltrexone to achieve three times the blood exposure of oral naltrexone. Teva's obviousness argument at trial therefore was that a double injection of the BioTek formulation discussed in the Comer paper *inherently* delivered the claimed AUC. But inherency requires more than probabilities or possibilities, and Teva was required to meet a very high legal standard that the claim limitation was the necessary result of the prior art. Teva's cross-study comparison, cherry-picking data from various, unrelated studies did not meet that standard.

Teva also did not clearly and convincingly show at trial that a POSA seeking to improve compliance compared to oral naltrexone, without hindsight knowledge of the '499 Patent, would have chosen a treatment that results in significantly higher blood exposure compared to oral naltrexone. Instead, Teva's obviousness argument ignored the risks of increasing exposure to naltrexone that an ordinarily skilled artisan, without hindsight, would have considered as potentially reducing compliance, such as the increased side effects of nausea, anxiety, and increased liver enzymes.

Teva also failed to prove by clear and convincing evidence that a POSA would have had a motivation from the prior art to treat dependence using a single injection of a long-acting formulation containing about 310-480 mg naltrexone. The highest naltrexone dose in a single injection of the BioTek formulation cited by Teva was 206 mg in the Kranzler paper, which was reported to be effective for alcohol dependence, but resulted in injection site reactions (indurations), leading Kranzler to recommend reducing the amount per injection. The subsequent Comer paper used 14 mg less naltrexone per injection (192 mg). The injections were given to persons receiving heroin, and Comer reported that two injections of 192 mg naltrexone resulted in "significantly elevated" cravings for heroin. Teva uses legally improper hindsight to find a reason for a POSA to treat a patient for heroin dependence using a single injection of the BioTek formulation with 384 mg naltrexone. Such hindsight is confirmed by the fact that the president of BioTek (Dr. Elie Nuwayser), who was a co-author of the Kranzler and Comer papers, subsequently filed for a patent describing the BioTek formulation, *but never claimed, made, or tested* a single injection of the BioTek formulation with 384 mg of naltrexone that Teva now asserts would have been obvious to a POSA.

Teva's attacks on the '499 Patent invention based on the language of Claim 1 fare no better. Teva failed to prove by clear and convincing evidence that a POSA reading the patent specification and prosecution history would not have reasonably understood (1) how to determine the AUC value for oral naltrexone, or (2) the time interval for calculating the AUC of a particular long-acting naltrexone formulation. The evidence at trial showed that a POSA would have understood how to calculate the AUC of oral naltrexone using a comparative PK study. Teva's counterevidence was based on flawed cross-study comparisons, a "common pitfall" that a POSA would have avoided as misleading. The time interval of the treatment period between administrations of the long-acting formulation matches the time interval for calculating the AUC, just as occurred in the Ehrich Declaration and the Tice patent. In any event, Teva's indefiniteness argument did not even apply to Claim 2 — which limits the time interval for that treatment to be four weeks.

Teva's alternative written description argument also failed. First, Teva invites legal error by suggesting nonobviousness and lack of written description are alternatives to one another. They are not — they are different defenses with different legal standards. Unlike an obviousness analysis, a written description analysis considers everything that has come before the patent *plus* what is written in the patent (*i.e.*, hindsight is allowed). The experts at trial agreed that the patent discloses a reproducible working example of the inventive method of treatment using a single injection of a long-acting naltrexone formulation achieving the claimed AUC profile.

Alkermes refers the Court to its Proposed Findings of Fact and Conclusions of Law for further details about the issues and evidence that were presented at trial.

## BACKGROUND

### I. The '499 Patent

#### A. Overview of the '499 Patent

The '499 Patent explains that the invention of the Asserted Claims is to provide a method of treating patients in need of naltrexone, using a long-acting formulation containing specified amounts of naltrexone and providing the claimed AUC, which “could be achieved by a single [intramuscular] administration.” ('499 Patent at .0007 (2:34-36); *see also* PFOF §§ III.A-D.)

The specification discloses preferred characteristics of the PLGA polymer for the claimed invention, including several examples of suitable extended release technologies, such as Medisorb<sup>®</sup>, Prolease<sup>®</sup> and Resomer<sup>®</sup>. (PFOF § III.A.) The '499 Patent's specification also teaches how to make and use such a formulation, and details the efficacy and safety of the method of treatment. (PFOF § III.A.) For instance, Example 1 uses the Vivitrol<sup>®</sup> formulation as illustrative of the claimed invention.<sup>1</sup> ('499 Patent at .0009-10 (5:36-8:2); *see also* PFOF § III.A.) The '499 Patent explains that Vivitrol<sup>®</sup> and other embodiments can be formulated by a manufacturing process discussed in Alkermes's patent referred to as “Wright,” which was incorporated into the specification by reference. (*See* '499 Patent at .0007-8 (2:63-3:33); *see also* PFOF § III.A.) Wright provided further details regarding the preferred characteristics of the PLGA polymer for the claimed invention. (*See* Wright at .0009 (7:50-8:60), .0011 (12:8-32); *see also* PFOF § III.A.)

The '499 Patent discloses significant Alkermes clinical trial data from successfully treating dependence using Vivitrol<sup>®</sup>. (PFOF §§ III.A, V.) For example, Example 2 includes an overview of the methods and results of the Phase III clinical trial of Vivitrol<sup>®</sup> in patients with alcohol

---

<sup>1</sup> The '499 Patent uses the name “Vivitrex” for the Alkermes formulation used in the Phase III clinical trials, which were used to obtain FDA approval of Vivitrol<sup>®</sup>. The name was modified in the course of obtaining FDA approval. (PFOF ¶ 55 n.4.)

dependence. (PFOF §§ III.A, V.) Example 3 discusses a comparison of efficacy with Vivitrol® versus oral naltrexone, including a conclusion that Vivitrol® “compares favorably with oral naltrexone.” (PFOF ¶¶ 56, 236.) Example 4 provides outcomes for the Phase III clinical trial, ALK21-003, including that the 380 mg dose versus placebo resulted in significantly improved health-related quality of life in alcohol-dependent patients, especially compared to the 190 mg dose versus placebo. (PFOF ¶ 57.) Example 5 discusses a one-year open-label extension study of ALK21-003, including results of that study, which confirmed the efficacy and tolerability of Vivitrol® for one year. (PFOF ¶ 58.)

#### **B. The Asserted Claims of the '499 Patent**

Claim 1 is made up of three components in combination: (1) treating individuals in need of naltrexone, (2) administering an injection of a long-acting formulation comprising about 310-480 mg naltrexone and PLGA (a biodegradable polymer), and (3) the long-acting formulation achieves a total blood exposure of naltrexone (AUC) that is about three times greater than that achieved by the standard 50 mg/day oral naltrexone dose. (PFOF § III.B.) With that context, a POSA would understand that a useful treatment of dependence using a long-acting injectable formulation, as in Claim 1, would be safe, effective, and tolerable. (PFOF § III.B.)

Dependent Claims 5 and 13 add more specificity to the requirements of the contents and performance of the formulation used in Claim 1. In Claim 5, the formulation must contain about 380 mg of naltrexone and the resulting serum AUC must be about 3.3 times greater than that achieved by 50 mg/day oral naltrexone administration. (PFOF § III.B.) In Claim 13, the formulation must have about 35% by weight naltrexone. (PFOF § III.B.)

Dependent Claims 2 and 10 add specificity to the treatment method. Claim 2 is limited to a treatment method that repeats use of a four-week long-acting formulation for 24 weeks. (PFOF § III.C.) Claim 10 is limited to treating persons afflicted by alcohol dependence. (PFOF § III.C.)

Teva stipulated that the use of its ANDA product infringes all of the Asserted Claims of the '499 Patent. (PFOF ¶ 9.)

**C. The Invention of Claim 1 is Limited to a Single Injection of a Long-Acting Formulation Containing the Specified Amount of Naltrexone**

It is well-established that a “validity analysis is a two-step procedure.” *TI Grp. Auto. Sys. (N. Am.), Inc. v. VDO N. Am., L.L.C.*, 375 F.3d 1126, 1139 (Fed. Cir. 2004). “The first step involves the proper interpretation of the claims. The second step involves determining whether the limitations of the claims as properly interpreted are met by the prior art.” *Id.* (overturning district court invalidity decision because the claim terms were construed incorrectly); *see also* COL § X.C. At trial, there was no genuine evidentiary dispute that Claim 1 of the '499 Patent requires a treatment method that administers a single injection of a long-acting formulation containing about 310-480 mg of naltrexone. (PFOF ¶¶ 74-77.)

A correct interpretation of the claims first requires consideration of the intrinsic evidence—*i.e.*, the claim language, the patent specification, and the prosecution history of the patent. *See, e.g., Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-14 (Fed. Cir. 2005) (*en banc*). As the intrinsic evidence at trial showed, a POSA would have understood that the plain language of Claim 1 and its dependent claims refers to an injection of a formulation containing the claimed amount of naltrexone, *i.e.*, the specified amount of drug contained in a single formulation given in a single injection. (PFOF § III.D; COL § X.C.) At trial, Teva’s witnesses did not offer a contrary opinion based on the actual language of the patent claim.<sup>2</sup> (PFOF ¶¶ 74-77.)

---

<sup>2</sup> Dr. Westreich *admitted* that he did not make his “own determination” about whether Claim 1 included multiple injections, but rather “took [his] understanding that the claims were not limited to a single administration of a naltrexone formulation from counsel.” (Westreich 174:3-15; *see also id.* at 99:11-16.)

The wording of the claim specifically refers to “the step of parenterally administering *a long-acting formulation comprising*” the specified amount of naltrexone. (’499 Patent at .0017 (Claim 1); *see also* PFOF § III.D.) The administration step must be of that formulation, where the words “step” and “formulation” are both in the singular context. *See, e.g., Insituform Techs., Inc. v. Cat Contracting, Inc.*, 99 F.3d 1098, 1104-5 (Fed. Cir. 1996) (where method comprised the “step[]” of using “a cup connected by a flexible hose to a vacuum source,” “nothing in the text of claim 1 suggests the use of more than one cup”); *Harari v. Lee*, 656 F.3d 1331, 1341 (Fed. Cir. 2011) (where claim refers to “a bit line” to activate a number of cells, “[t]he plain language of the claim clearly indicates that only a single bit line is used when accessing a number of cells”). As Dr. Little explained, a POSA reading Claim 1 would understand that it is in the context of “a single formulation,” and that “single formulation would comprise” the claimed dose of naltrexone. (Little 793:1-5; *see also* PFOF § III.D.)

The dependent claims can help inform the meaning of an independent claim. *See, e.g., Phillips*, 415 F.3d at 1314. Here, the dependent claims confirm that Claim 1 is in the context of a single injection of a formulation containing the specified amount of naltrexone. Dependent Claims 2, 5, and 13 recite “*the* long acting formulation” of Claim 1 used in the treatment method. (PFOF § III.D.) Again, the use of the word “the” is singular, further confirming the single formulation containing the specified dosage amount of Claim 1.

The Federal Circuit has also made clear that “[w]e cannot look at the ordinary meaning of the term . . . in a vacuum. Rather, we must look at the ordinary meaning in the context of the [patent specification] and the prosecution history.” *Phillips*, 415 F.3d at 1313 (citation and internal quotation marks omitted) (alteration in original).

The '499 Patent specification confirms that the plain language of Claim 1 is in the context of a single injection of a formulation containing the claimed amount of naltrexone. (PFOF § III.D.) When providing a summary of the invention, the specification explains that the claimed AUC is “achieved by a *single* [intramuscular] administration.” ('499 Patent at .0007 (2:34-36) (emphasis added); *see also* PFOF ¶¶ 71-72.) Further, all of the examples in the specification discuss a single injection of a formulation containing the claimed amount of drug for treatment. (PFOF ¶¶ 71-72.) As Dr. Westreich *admitted*, the '499 Patent specification does not describe “administration of a long-acting formulation of naltrexone split up into multiple injections.” (Westreich 177:1-5.)

Finally, the patent prosecution history is dispositive of the correct claim construction. (PFOF ¶ 73.) The inventor, Dr. Ehrich, submitted a declaration where he expressly stated: “*The present invention is directed to . . . a single injection of a naltrexone-containing long-acting formulation.*” (Ehrich Declaration at .0001 (emphases added).) Dr. Westreich likewise admitted that Dr. Ehrich described his invention in the prosecution history as “an unexpected discovery with regard to *a single injection* of naltrexone” (Westreich 176:22-25 (emphasis added)), and that the prosecution history does *not* describe “the administration of a long-acting formulation of naltrexone split up into multiple injections” (Westreich at 177:6-10).

This construction must, as a matter of law, be applied when considering whether Teva proved by clear and convincing evidence that the invention of Claim 1 would have been obvious to an ordinarily skilled artisan without hindsight as of April 2004. (COL § X.C.)

## **II. Overview of the Prior Art Search for a Treatment of Alcohol and Opioid Dependence Using a Long-Acting Naltrexone Formulation as of 2004**

Alcohol and opioid dependence are a subset of substance use disorders and are chronic psychiatric conditions that have significant effects on patients' overall well-being, quality of life, and mortality. (PFOF § IV.A.) Both alcohol and opioid dependence are characterized by

uncontrollable, recurring cravings, which can include physical and physiological dependence. (PFOF § IV.A.) At the time of the invention, naltrexone in an oral tablet form (ReVia<sup>®</sup>) was available to treat alcohol and opioid dependence.<sup>3</sup> (PFOF §§ IV.A-B, IV.C.1.) The experts at trial agreed that the FDA-approved dosage of 50 mg/day was the recognized “optimal dose” of oral naltrexone. (PFOF § IV.C.10, ¶ 156 n.16.)

It is undisputed that oral naltrexone was plagued by noncompliance issues for decades after it was first approved by the FDA in 1984. (PFOF §§ IV.A-C, VI.A.) As the evidence at trial established, taking a daily pill for the treatment of substance use disorders like alcohol and opioid dependence is not a simple matter, especially for patients experiencing cravings and other side effects like nausea, anxiety, and increased liver enzymes. (PFOF § IV.A.) Accordingly, as Teva’s expert Dr. Westreich acknowledged, “a POSA in 2004 would have been looking for a long-acting naltrexone treatment that was safe and effective and would improve patient compliance compared to oral naltrexone.” (Westreich 178:7-11; *see also* PFOF §§ IV.A-C, VI.A.) A long-acting injectable naltrexone formulation had the potential to be a better treatment for alcohol and opioid dependence compared to oral naltrexone *if* it was demonstrated to be safe and effective, and had sufficient tolerability and avoidance of side-effects such that patients would actually comply with a regimen of long-acting injections. (PFOF §§ IV.A-C, VI.A.)

As early as the Olsen paper in 1981, NIDA<sup>4</sup> recognized the seriousness of the compliance issue, and called on researchers to create an effective, long-acting naltrexone formulation, where a single administration would last for a month. (PFOF §§ IV.B, IV.C.2.) As it turned out, however,





---

<sup>3</sup> Naltrexone is an opioid antagonist, which means it inhibits opioid receptors in the brain. (PFOF ¶ 83.)

<sup>4</sup> NIDA is a division of the National Institutes of Health, with the mission to advance science on addiction and to apply that knowledge to improve individual and public health.

treating individuals with a long-acting injection of naltrexone presented challenges, and the 1981 Olsen paper was followed by decades of exploration of several long-acting naltrexone formulations by a few researchers, none of which resulted in a successful treatment. (PFOF §§ IV.B, IV.C, VI.A.) For example, in Chiang 1984 and Chiang 1985, NIDA researchers prepared polymer beads with naltrexone, which were able to antagonize (or block) the effects of heroin, but adverse effects at the site of injection (*e.g.*, “extrud[ing],” “marked inflammatory reaction that became indurated,” and “incidence of tissue irritations of the naltrexone beads”), precluded their clinical utility as a treatment method. (Chiang 1984 at .0004; Chiang 1985 at .0007; *see also* PFOF §§ IV.B, IV.C.3-4.)

From 1994 through 2001, the Heishman, Alim, Kranzler, and Comer publications discussed experiments with long-acting formulations made by BioTek containing various amounts of naltrexone, which Teva collectively referred to at trial as “Depotrex”:

Timeline of BioTek Studies					
	1994 Heishman  DTX-216	1995 Alim  DTX-124	1998 Kranzler  DTX-217	2001 Comer  DTX-9	
Subjects	Four No dependence	Four / Four Cocaine dependence + received morphine	Twenty Alcohol dependence	Six / Six Heroin dependence + received heroin after detoxification	
Injections	1 injection	1 injection	1 injection	1 injection	2 injections
Naltrexone	52 mg	103 or 206 mg	206 mg	192 mg	192 mg 192 mg
Results	Safe to proceed with higher dose	Variable responses to morphine and recommended testing in detoxified subjects with opioid use disorder	Has effect but <i>suggested reduced amount per injection</i>	Antagonism for at least three weeks	Longer antagonism but <i>dramatically higher cravings for heroin than one injection</i>
	PTX-23 / DTX-216		PTX-25 / DTX-217	PTX-18 / DTX-9	
	PDX-203				

(*See* Weiss 592:24-594:5 (discussing PDX-203); *see also* PFOF §§ IV.B, IV.C.5-8.)

According to Dr. Westreich, the 1998 Kranzler paper reported that a single injection of the BioTek formulation containing 206 mg naltrexone “could be effective when administered every four weeks for alcohol dependence.” (Westreich 181:12-14; PFOF ¶ §§ IV.B, IV.C.7.) As Dr. Westreich acknowledged, however, about “73 percent of those subjects had induration[s] around their injection site,”<sup>5</sup> and those “indurations ranged from 1 to 5 weeks with an average of 2.8 weeks.” (See Westreich 181:24-182:8; see also Weiss 552:8-553:24 (explaining this “worrisome finding” that could result in decreased compliance); PFOF §§ IV.B, IV.C.7.) This result, as Dr. Westreich admitted, led the authors to conclude that “by *reducing the total dose of naltrexone* in each injection, the volume injected and the peak plasma concentration would be reduced, which would *reduce adverse effects*.” (Westreich 183:14-20 (emphases added); see also PFOF §§ IV.B, IV.C.7.)

No further prior art studies with the BioTek formulation were done with respect to persons suffering from alcohol dependence after the Kranzler paper. (PFOF § IV.B.) And BioTek never used a formulation containing more than 206 mg naltrexone in any person afflicted with alcohol dependence. (PFOF § IV.B.)

Teva’s last prior art study using long-acting naltrexone was the 2001 Comer paper, in which Dr. Comer, the president of BioTek (Dr. Nuwayser), and other researchers published a small study giving long-acting naltrexone to heroin-dependent subjects who were also given heroin during the study. (PFOF §§ IV.B, IV.C.8.) Dr. Comer reported that “[t]he active formulation contained drug equivalent to 192 mg naltrexone base,” which means the injection of the formulation in fact had a reduced amount of naltrexone compared to Kranzler, *i.e.*, 14 mg less naltrexone in the injection. (Comer at .0010; see also PFOF §§ IV.B, IV.C.8.) Dr. Comer gave

---

<sup>5</sup> An induration is a thickening or hardening of the tissues around an injection. (PFOF ¶ 174 n.19.)

one or two injections of the 192 mg formulation (when two naltrexone injections were given, one was given in each buttock). (PFOF §§ IV.B, IV.C.8.)

Dr. Comer measured the antagonistic effects of heroin, finding that the single injection of 192 mg naltrexone antagonized the effects of heroin for three weeks, and the two injections of 192 mg naltrexone antagonized the effects of heroin for five weeks. (PFOF §§ IV.B, IV.C.8.) But, the two injections of 192 mg of naltrexone also had a “dramatic difference” in cravings for heroin. (Comer at .0011, .0014; *see also* PFOF §§ IV.B, IV.C.8.) Cravings for heroin were significantly *increased* in the two-injection group as compared to the one injection group. (PFOF §§ IV.B, IV.C.8.) On direct, Dr. Westreich did not address the Comer paper’s discussion of these results. On cross-examination, however, he agreed that “the 192-milligram depot form of naltrexone *performed better* than the 384-milligram depot form of naltrexone” with respect to the report of cravings for heroin. (Westreich 203:23-204:4 (emphasis added).) Put simply, a POSA would not have treated persons dependent on heroin in a way that was reported to cause high cravings for heroin. (PFOF § IV.C.8.)

The Comer paper did not study or show successful treatment of persons afflicted by heroin dependence, and expressly reports that subjects were excluded from the study if they were seeking drug treatment or were dependent on alcohol. (PFOF §§ IV.B, IV.C.8.) Dr. Westreich agreed that he was not offering an opinion that the Comer paper taught “that any person emerging from the study was less dependent on heroin than when they started.” (Westreich 188:13-16; *see also* PFOF §§ IV.B, IV.C.8.)

The Comer paper concluded that “[f]uture studies” would be needed to “evaluate the clinical utility of depot naltrexone in the treatment of heroin dependence.” (Comer at .0015; *see also* PFOF § IV.C.8.) But according to Dr. Westreich, the next BioTek publication, the Nuwayser

patent, “has no information on the use of a naltrexone formulation other than the copy” of Figure 1 from the Comer paper.<sup>6</sup> (Westreich 209:24-210:2; *see also* PFOF §§ IV.B, IV.C.9.) The Nuwayser patent “did not describe any new uses of the BioTek formulation for naltrexone” (Westreich 209:3-5), and did not “describe the creation of a new formulation that has 384 [mg] of naltrexone for injection” (Westreich 211:18-21; *see also* Yaman 428:5-13 (Dr. Yaman admitting that he “did not point to any instance where Nuwayser, based on Comer, decided to put 384 [mg] in one injection”)). (PFOF §§ IV.B, IV.C.9.) Instead, the Nuwayser patent was focused on methods for preparing multi-layer microcapsules and discussed a long-list of more than 25 different potential active ingredients (only one of which was naltrexone). (PFOF §§ IV.B, IV.C.9.)

Mr. Kerrigan<sup>7</sup> confirmed that, even internally at BioTek, they never made a single formulation of long-acting naltrexone containing the amount of naltrexone in the Asserted Claims. (PFOF §§ IV.B, IV.C.9.) Instead, as Mr. Kerrigan described it, the formulations “all contain around 200 [mg] per dose.” (Kerrigan (5/3/22) Tr. 45:7-45:13.) The evidence at trial confirmed that BioTek never advanced into “Phase III clinical trials” with a long-acting naltrexone formulation and never reached its development goal of “an injectable naltrexone product that can be prescribed to humans.” (Kerrigan (5/3/22) 55:4-7, 55:20-23; PFOF §§ IV.B, IV.C.9.)

### **III. Alkermes’s Development and Dr. Ehrich’s Theory That Made Vivitrol® Possible**

Dr. Ehrich explained at trial his personal motivation for seeking a significantly higher blood exposure compared to oral naltrexone, which Teva did not show was discussed in any prior art literature. (PFOF § V.) Dr. Ehrich testified that he had a novel hypothesis in which he saw

---

<sup>6</sup> Dr. Nuwayser was co-author on the Kranzler and Comer papers. (PFOF ¶ 119.)

<sup>7</sup> Mr. Kerrigan was a former BioTek employee, who was hired by Teva as a witness for this case. (PFOF ¶ 48.) He provided his testimony during a *de bene esse* deposition. (*See generally* DTX-241.)

dependence as a “significant alteration of the brain’s reward system” caused by “endogenous opioid dysregulation.” (PFOF § V.) He theorized that a significantly higher exposure to naltrexone could “rebalance altered wiring in the brain” to try to impact the “broken reward system” of patients in need of naltrexone. (PFOF § V.)

Dr. Ehrich had been involved in clinical trials at Alkermes using long-acting naltrexone from the time he joined the company in 2000. (PFOF § V.) Based on his theory and the data available to him at Alkermes, Dr. Ehrich designed a Phase III clinical trial (ALK21-003) testing two doses of naltrexone, 190 mg and 380 mg, each to be given in a single injection every 28 days. (PFOF § V.) Based on Alkermes’s earlier research, Dr. Ehrich selected 190 mg because he felt it would provide “somewhat greater” exposure of naltrexone compared to the 50 mg/day oral dosing regimen, and 380 mg because it would provide “approximately three-fold higher” exposure compared to the oral dose. (PFOF § V.) Dr. Ehrich’s idea to include a 380 mg dose, however, received pushback internally at Alkermes. (PFOF § V.) Those critics believed that Alkermes should focus on replicating the 50 mg/day oral dose with the 190 mg injection, including because higher doses were known to be associated with higher risks of side effects. (PFOF § V.) Dr. Ehrich decided to push forward over the objections of his colleagues, and include the additional dose of 380 mg in the Phase III clinical trial, despite the greatly increased size, duration, complexity, and cost of the study that resulted from moving forward with the additional dose. (PFOF § V.)

The results of ALK21-003 and various other studies validated Dr. Ehrich’s hypothesis — *i.e.*, treating a patient in need of naltrexone with an injection of a long-acting formulation containing PLGA and achieving an AUC that is about three times higher than that achieved by 50

mg/day oral naltrexone — was a safe and effective treatment for alcohol and opioid dependence.<sup>8</sup> (PFOF § V.) Dr. Westreich agreed that the results of ALK21-003 were “persuasive for a provider to appreciate the benefits of the 380-milligram dose compared with the 190-milligram dose.” (Westreich 223:16-224:2.)

Today, Vivitrol<sup>®</sup> remains the first and only long-acting injectable naltrexone formulation shown to have been effective in the treatment of alcohol dependence and for the prevention of relapse to opioid dependence. (PFOF §§ V, VII.A.) Vivitrol<sup>®</sup> is prescribed for use as a single injection of a long-acting formulation containing 380 mg of naltrexone, once monthly. (PFOF §§ V, VII.A.) The FDA approved label for Vivitrol<sup>®</sup> includes a reference to the significantly higher AUC compared to oral naltrexone. (PFOF § VII.A.) Dr. Westreich agreed that “for the most part, when [he] prescribe[s] naltrexone, [he] prescribe[s] Vivitrol,” and he does so “because of the benefits that Vivitrol offers to patients over oral naltrexone.” (Westreich 228:13-18.)

## ARGUMENT

### **I. Teva Did Not Prove by Clear and Convincing Evidence that the Asserted Claims Would Have Been Obvious To a POSA at the Time of the Invention**

#### **A. Teva Bears the Heavy Burden of Proving Obviousness by Clear and Convincing Evidence**

“A patent shall be presumed valid” and “[e]ach claim of a patent . . . shall be presumed valid independently of the validity of other claims.” 35 U.S.C. § 282; *Microsoft Corp. v. i4i Ltd. P’ship*, 564 U.S. 91, 97 (2011). Under 35 U.S.C. § 103, a patent claim is valid unless the accused infringer proves that the differences between the claimed subject matter and the prior art are such that the claimed subject matter as a whole would have been obvious to a POSA at the time of the

---

<sup>8</sup> After receiving initial data from ALK21-003 in late 2003 and conducting analyses of the data in early 2004, Dr. Ehrich’s provisional patent application for his invention was submitted on April 22, 2004. (PFOF ¶¶ 140, 146.)

invention. *See* 35 U.S.C. § 103(a). In conducting an analysis of an obviousness defense, the following factors must be considered: the scope and content of the prior art; the differences between the prior art and the claimed invention; the level of ordinary skill in the art; and any objective indicia of nonobviousness, including long-felt but unmet need, failure of others, skepticism, unexpected properties, and copying. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *see also* COL § X.D.1.

The Federal Circuit has warned of “fall[ing] victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher.” *In re Kotzab*, 217 F.3d 1365, 1369 (Fed. Cir. 2000); *see also* COL § X.D.1. If hindsight works its way into the analysis, a conclusion of obviousness will be legal error. *See, e.g., In re Cyclobenzaprine*, 676 F.3d 1063, 1073 (Fed. Cir. 2012). Moreover, an infringer cannot try to point to the inventors’ own work as supporting obviousness, since “[p]atentability shall not be negated by the manner in which the invention was made.” 35 U.S.C. § 103; *see also Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012) (“The inventor’s own path itself never leads to a conclusion of obviousness; that is hindsight. What matters is the path that the [POSA] would have followed, as evidenced by the pertinent prior art.”).

## **B. The Problem Facing a POSA in 2004**

The evidence at trial established that a POSA<sup>9</sup> in April 2004 would have understood that 50 mg/day oral naltrexone “was effective for the treatment of alcohol and opioid abuse.”

---

<sup>9</sup> The level of skill of the POSA is a B.S. in the pharmaceutical sciences or a related discipline (*e.g.*, chemistry) with four to five years of experience developing sustained-release drugs using biocompatible polymers. (PFOF ¶ 145.) The POSA can also consult a member of a multi-disciplinary team in relevant disciplines that lie outside the POSA’s area of primary training. (PFOF ¶ 145.) The relevant date to consider for the time of the invention is April 22, 2004, which was the filing date of the provisional application that led to the ’499 Patent. (PFOF ¶ 146.)

(Westreich 177:13-21; *see also* PFOF § VI.A.) But because it required the patient to make the choice of taking it every day, “[p]rior to 2004, oral naltrexone was associated with poor patient compliance and a high early dropout rate,” and “as of 2004, the established naltrexone treatment was still considered by those of ordinary skill in the art to be plagued by patient compliance issues.” (Westreich 177:25-178:6; *see also* PFOF § VI.A.) In light of this need for a new or improved treatment for alcohol or opioid dependence (*see supra* Background § II), “a POSA in 2004 would have been looking for a long-acting naltrexone treatment that was safe and effective and would improve patient compliance compared to oral naltrexone” (Westreich 178:7-11; *see also* PFOF § VI.A; COL § X.D.2).

If a POSA was focused on developing a long-acting formulation of naltrexone as Teva’s witnesses assert, a POSA would have wanted to match exposure to the FDA-approved oral naltrexone treatment of 50 mg/day, which the Leavitt article expressly acknowledged as “optimal” (Leavitt at .0006), and the Comer paper discussed as the “standard dose” used for clinical treatment (Comer at .0014).<sup>10</sup> (PFOF § VI.A.) Increasing the level of exposure by three-fold as taught by the ’499 Patent would mean a POSA departed from the established safety and efficacy of oral naltrexone, which could, without hindsight, have been thought to exacerbate the known side effects associated with naltrexone such as nausea, anxiety, or increased liver enzymes. (PFOF ¶¶ 170, 195.)

---

<sup>10</sup> The Tice patent provides an example of the prior art pointing a POSA toward developing a long-acting formulation with “*comparable* exposure” to 50 mg/day oral naltrexone. (PFOF ¶¶ 169, 195.) As Dr. Yaman agreed, a POSA would have believed that Tice is claiming “to solve the patient compliance issue with a new long-acting naltrexone formulation.” (Yaman 406:4-8.)

**C. Teva Did Not Prove By Clear and Convincing Evidence That Claims 1 and 5 Would Have Been Obvious Over Comer, Nuwayser, and Leavitt**

Teva's obviousness defense at trial was that a POSA as of April 2004 would have been motivated to combine Comer, Nuwayser, and Leavitt to arrive at the inventions of Claims 1 and 5 with a reasonable expectations of success. (*See* D.I. 198; *see also* PFOF ¶ 78.) For each of the independent reasons discussed below, however, Teva failed to prove by clear and convincing evidence that Claims 1 and 5 would have been obvious in light of the problem facing a POSA. (COL §§ X.D.1-3.)

**1. Teva Failed to Prove that a POSA Would Have Been Motivated to Treat Opioid or Alcohol Dependence With a Single Injection of a Long-Acting Formulation Containing the Claimed Amount of Naltrexone that Achieves the Claimed Naltrexone Exposure**

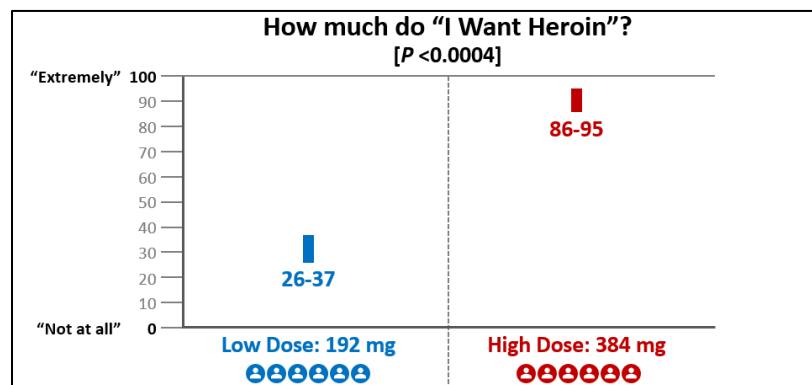
Teva's witnesses asserted that a POSA facing the problem of improving patient compliance with oral naltrexone would have been motivated to: (1) start with the 192 mg long-acting naltrexone formulation discussed in the Comer paper; (2) focus on the double injection of the formulation and reformulate it into a single injection totaling 384 mg, and (3) use that single injection of 384 mg to treat dependence. This argument erroneously picks and chooses from among prior art references using hindsight knowledge of the use of Alkermes's Vivitrol®.<sup>11</sup> *See Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 921 (Fed. Cir. 2011) ("[I]t is impermissible [as part of the obviousness analysis] to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art."); *see also* COL §§ X.D.1, X.D.3.

---

<sup>11</sup>Dr. Westreich and Dr. Yaman's opinions actually promoted improper hindsight thinking by deliberately using the present tense, arguing that the invention "is obvious." (PFOF ¶ 154 n.13.)

*First*, Drs. Westreich and Yaman asserted that a POSA would have focused on the two injections of the formulation (totaling 384 mg) discussed in the Comer paper because it antagonized effects of heroin for five weeks when the single injection of the 192 mg formulation antagonized effects for three weeks.<sup>12</sup> (PFOF ¶ 155.) But in reaching their opinion, both of Teva’s witnesses ignored an express finding by the authors of the Comer paper, identified as “dramatic,” that would have dissuaded a POSA from the higher amount as a treatment for dependence: the higher 384 mg dose resulted in “significantly elevated” cravings for heroin compared to the 192 mg lower dose group. (PFOF §§ IV.C.8, VI.B.1.)

The evidence at trial undisputedly showed that Comer taught a “dramatic difference” in cravings for the high dose group, as seen below:



(See Weiss 572:15-20, 575:19-576:22 (discussing PDX-202); see also PFOF ¶¶ 116-118, 158-164.) Based on these data, Dr. Westreich admitted that “*the 192 [mg]* depot form of

<sup>12</sup> Dr. Yaman opined that a POSA would have been motivated to select the higher dose to “target[] a minimum plasma naltrexone level of 2 [ng/mL]” based on an old Verebey reference. (PFOF ¶ 155 n.15.) But if a POSA was following Comer, that POSA would also be following Comer’s teachings rejecting Verebey and finding that “negligible” blood plasma levels of naltrexone (around 0.3 ng/mL) antagonized heroin’s effects. (PFOF ¶ 155 n.15.) Comer did not find that 2 ng/mL was the minimum therapeutic level of naltrexone, as Teva argues using hindsight. Further, Teva failed to establish that a POSA would have either.

naltrexone *performed better* than the 384 [mg] depot form of naltrexone studied in Comer for that rating criteria.” (Westreich 203:23-204:4; *see also* PFOF ¶¶ 158-164.)

This is no minor observation for a POSA to see in the Comer paper. Dr. Westreich admitted that “one of the things that you try to treat patients for that are suffering from opioid abuse is their cravings for heroin.” (Westreich 204:5-8; *see also* PFOF ¶¶ 158-164.) In other words, a POSA with the goal of treating dependence would want to *minimize* cravings because increasing cravings would be detrimental to patient compliance.

*Second*, Teva failed to prove that a POSA would have been motivated to treat a patient with a long-acting naltrexone formulation that achieved about three (or about 3.3) times higher total exposure compared to oral naltrexone. (PFOF ¶¶ 165-170.) If a POSA was focused on developing a long-acting formulation to improve compliance compared to oral naltrexone (*see supra* Argument § I.B), without the benefit of hindsight, a POSA would not have been motivated to increase the level of exposure by three-fold. As Dr. Westreich admitted, he “did not identify *any* prior art reference that discusses the pursuit of a depot form of naltrexone that has a three times greater plasma AUC than oral naltrexone.”<sup>13</sup> (Westreich 207:16-19.) Increasing the exposure without any good reason to do so would have required a POSA to depart from the established safety and efficacy of oral naltrexone, which could exacerbate the known side effects associated with naltrexone itself, such as nausea, anxiety, or increased liver enzymes.<sup>14</sup> (PFOF ¶¶

---

<sup>13</sup> Dr. Westreich *admitted* that “the only document from 2004 or earlier [he] identified that actually compared the AUC of a long-acting naltrexone formulation to the AUC of an oral formulation” was the Tice patent. (Westreich 207:11-19.) In Tice, however, the goal was a treatment using a long-acting formulation that provided “*comparable* exposure of naltrexone” to 50 mg/day oral naltrexone. (PFOF ¶¶ 169, 195.)

<sup>14</sup> Although the Comer paper states that certain side effects were not observed, this was only in six subjects, who received a round of naltrexone injections and were also receiving increasing doses of heroin. As Dr. Weiss explained, a POSA could not rule out side effects for a larger group from the nature of this small preliminary study. (PFOF ¶ 198.)

165-170; COL §§ X.D.1-3.) Dr. Westreich agreed that “as of 2004, scientists in the art felt that naltrexone did induce adverse neuropsychiatric and gastrointestinal effects.” (Westreich 196:12-15.) Such a departure would have directly conflicted with Teva’s asserted motivation for a POSA to develop a long-acting formulation in the first place. (COL §§ X.D.1, X.D.2, ¶ 288.)

**Third**, even if a POSA would have been motivated to pursue the higher 384 mg dose of the BioTek formulation for treating a patient with dependence (which Teva did not establish by clear and convincing evidence), Teva failed to prove that a POSA would have done so with a single injection of 384 mg of naltrexone — as required by Claims 1 and 5 (*see supra* Background § I.C). (PFOF ¶¶ 171-178.) The conclusory and unsupported testimony of Teva’s witnesses that it would not “be difficult to change from two injections to one injection” (Westreich 100:19-21), ignores that these were injections of polymer microcapsules — the prior art did not ever show use of more than 206 mg naltrexone in a single injection of the BioTek formulation and, in fact, identified reasons not to do so.

The highest dose of naltrexone in the BioTek formulation tested in a single injection in the prior art was 206 mg in the Kranzler paper. (PFOF ¶¶ 171-178.) As Dr. Westreich acknowledged, the Kranzler paper reported about “73 percent of those subjects had induration[s] around their injection site,” and those “indurations ranges from 1 to 5 weeks with an average of 2.8 weeks.” (Westreich 181:24-182:8.)<sup>15</sup> This result, as Dr. Westreich admitted, led the authors to conclude that “*reducing the total dose of naltrexone . . . would reduce adverse effects.*” (Westreich 183:14-20 (emphases added); Kranzler at .0005.)

---

<sup>15</sup> Drs. Yaman and Westreich focused on Kranzler’s discussion of side effects during the “follow up period” that were “comparable to that of oral.” (PFOF ¶ 174 n.19.) But that testimony ignored Kranzler’s next reported conclusion regarding indurations that occurred in the treatment period. This is unlike oral naltrexone (as a pill taken by mouth), which does not cause indurations — a painful hardening of the skin at the site of injection. (PFOF ¶ 174 n.19.)

Assuming, as the law requires, that a POSA has no hindsight knowledge of Alkermes's invention, the Kranzler paper's conclusion of "**reducing** the total dose of naltrexone in each injection" would certainly have discouraged a POSA from **increasing** the total dose per injection by **almost double**, to 384 mg of naltrexone per injection, to develop an improved treatment that increased patient compliance. *See, e.g., Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1306 (Fed. Cir. 2015) ("An inference of nonobviousness is especially strong where the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements."); *see also* COL ¶ 288. As Dr. Weiss explained, "if nobody is going to take [the injection] a second time," it is not going to be an "effective treatment." (Weiss 553:13-24.)

Further demonstrating the lack of motivation without hindsight to develop a single injection of 384 mg naltrexone, Dr. Westreich confirmed that the next BioTek publication after the Comer paper (the Nuwayser patent), does not "describe the creation of a new formulation that has 384 [mg] of naltrexone for injection." (Westreich 211:18-21; *see also* PFOF ¶ 177.) Despite Dr. Yaman's hindsight assertion that "the next phase of product development would be to try to put the 384 [mg] into one injection" after the Comer paper (Yaman 428:5-9), he admitted that he "did not point to any instance where Nuwayser, based on Comer, decided to put 384 [mg] in one injection" (Yaman 428:10-13).

There was no motivation in the prior art for a POSA to do what the Comer and Nuwayser publications in fact did not do — administer a single injection of a long-acting formulation containing 384 mg of naltrexone in a PLGA polymer. (PFOF ¶¶ 171-178.)<sup>16</sup> Nor was there any

---

<sup>16</sup> Mr. Kerrigan even confirmed that BioTek never made or tested a single formulation of long-acting naltrexone around 380 mg. (PFOF ¶¶ 178.) Instead, the BioTek formulations "all contain around 200 [mg] per dose." (Kerrigan (5/3/22) Tr. 45:7-13; *see also* PFOF ¶¶ 98-99, 121, 178.)

evidence of BioTek working toward a method of treatment requiring two injections, one in each buttock, every month as a treatment method to *improve* compliance over oral naltrexone.

**2. Teva Failed to Prove By Clear and Convincing Evidence That the Claimed Naltrexone Exposure Was Inherent to the Dose of Naltrexone In a Long-Acting Formulation**

Dr. Westreich candidly admitted that Teva “did not identify any prior art reference that discusses the pursuit of a depot form of naltrexone that has a three times greater plasma AUC than oral naltrexone.” (Westreich 207:16-19.) Instead, Dr. Yaman testified that the claimed naltrexone exposure was inherent in a 384 mg dose of naltrexone in a long-acting formulation with PLGA. (Yaman 330:9-19; *see also* PFOF § VI.B.2.) But inherency requires that a result is necessary and inevitable, and Dr. Yaman’s speculation that amounts to only “probabilities or possibilities” is insufficient to demonstrate a result is inherent by clear and convincing evidence. (COL ¶ 289.)

The Federal Circuit has warned that there is “a high standard in order to rely on inherency to establish the existence of a claim limitation in the prior art in an obviousness analysis,” and “[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient to render the result inherent.” *Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1367 (Fed. Cir. 2017); *see also Endo Pharm. Solutions v. Custopharm Inc.*, 894 F.3d 1374, 1381 (Fed. Cir. 2018) (a party cannot rely on “probabilities or possibilities,” but must show that the claim limitation at issue is “necessarily” present in the prior-art combination).

Dr. Yaman admitted that the dose of naltrexone alone does not dictate the resulting AUC of a long-acting formulation with PLGA. (PFOF ¶ 180.) For example, Dr. Yaman agreed that a POSA has a number of tools that change the AUC without changing the dose, including “lower[ing] the molecular weight,” “which translates to a faster release rate” (Yaman 415:14-22), as well as “vary[ing] the ratio of glycolic acid to lactic acid to affect release rate” (Yaman 416:7-

14).<sup>17</sup> In other words, where changes to the formulation itself (without changing the dose) will change the “release rate and blood plasma levels” (Yaman 410:23-411:4), an AUC is not necessarily the “direct result” of the dose, but rather a possibility. Of course, once the goal has been expressly taught by Alkermes’s ’499 Patent (*i.e.*, about three times AUC), the POSA can now use the information to design the formulation for the treatment method (*see infra* Argument § III). For Teva’s defense of obviousness, however, the POSA cannot have hindsight knowledge or know of the goal, which Dr. Westreich admitted was not taught in the prior art.

Dr. Yaman’s entire opinion that the claimed naltrexone exposure was silently inherent in the Comer study was based on cherry picking *cross-study comparisons* between data reported in the Comer paper, for a set of individuals who were addicted to heroin and who were given heroin and long-acting naltrexone, and data reported in “*unrelated studies*” with no similarity to the Comer study for people receiving oral naltrexone. (Yaman 400:7-10 (emphases added); *see also* PFOF ¶¶ 181-186.) As the evidence at trial showed, including testimony from Dr. Peck regarding the well-respected technical literature in the art, such a cross-study comparison is a “common pitfall” that should be avoided because any results “can lead to false conclusions.” (*See* Remington at .0008-10; *see also* PFOF ¶¶ 183-184.) None of Teva’s experts testified that a cross-study comparison would have been an accepted methodology to a POSA as of April 2004 for calculating comparative AUC values. Dr. Yaman actually testified to the opposite, stating: “[T]he outcome of the calculation depends on which oral AUC value you happen to use,” because “it’s gonna

---

<sup>17</sup> The Tice patent provides an example of how the dose of a long-acting naltrexone formulation is not determinative of the resulting AUC. In particular, Tice described a long-acting naltrexone formulation with 300 mg of naltrexone, which resulted in an AUC that was comparable to 50 mg/day of oral naltrexone. (PFOF § IV.C.11, ¶¶ 169, 180 n.23, 195.)

greatly impact the outcome.” (Yaman 301:22-25; *see also* PFOF ¶¶ 183-184.)<sup>18</sup>

The POSA would also have understood that the plasma data reported in the Comer paper was not appropriate for calculating the AUC of the long-acting formulation compared to 50 mg/day oral naltrexone because, as Dr. Westreich admitted, the Comer paper “was not conducted to be a pharmacokinetic comparison between oral naltrexone and long-acting naltrexone.” (Westreich 195:14-17; *see also* PFOF ¶ 185.) For example, the Comer paper was conducted in heroin-dependent individuals receiving heroin — not healthy subjects — which is not how the AUC property of a given formulation would be determined. (PFOF ¶ 185.) Even if Teva could show that the AUC was “probable” or “possible” from the Comer study that would *still not satisfy the legal standard for inherency*, which requires proving, by clear and convincing evidence, that the comparative AUC is *necessarily* present in the Comer study. (COL ¶ 289.)

And even if Teva had proven the AUC was necessarily present in the Comer study, it still did not prove that the AUC would have been necessarily present if the Comer study had given a *single* injection of a BioTek long-acting formulation containing around 380 mg of naltrexone, as required by Claim 1 and 5. (COL § X.D.3.) There was no such BioTek formulation in the prior art.

### **3. Teva Failed to Prove By Clear and Convincing Evidence that a POSA Would Have Had a Reasonable Expectation of Success of the Claimed Invention Based on the Combination of Comer, Nuwayser, and Leavitt**

An assertion of obviousness requires not just clear and convincing evidence that a POSA, without hindsight, would have combined and modified the prior art to arrive at the claimed

---

<sup>18</sup> That Dr. Yaman selected data from unrelated studies with the hindsight knowledge of Alkermes’s invention is further demonstrated by the fact that he ignored oral AUC values from other studies that did not necessarily result in about three (or about 3.3) times greater AUC. (PFOF ¶ 184.)

invention, but also that such a POSA would have had a reasonable expectation of success in doing so. *Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859-61 (Fed. Cir. 2015); *see also* COL § X.D.1, ¶ 290.

Drs. Westreich and Yaman provided only conclusory testimony regarding reasonable expectation of success for a treatment method, asserting that Comer, Nuwayser, and Leavitt “result in, essentially, the claims” (Yaman 344:6-10), and “talk about the use of naltrexone to treat alcohol use disorders or opioid use disorder” (Westreich 105:8-18.) This type of testimony is insufficient as a matter of law. *See, e.g., Amgen Inc. v. F. Hoffmann-La Roche, Ltd.*, 580 F.3d 1340, 1363 (Fed. Cir. 2009) (affirming that expert testimony based on the claims themselves, and the inventor’s personal expectations, did not support a finding of reasonable expectation of success); *see also* COL ¶ 295.

The Comer paper was a small study that explored the antagonistic effects of the BioTek formulation in heroin-dependent subjects who received heroin as part of the study. It was not designed or intended to show safety and efficacy, or improved compliance, for a treatment method, and expressly excluded subjects from the study if they were seeking treatment and excluded individuals whose drug of choice was alcohol. (PFOF §§ IV.C.8, VI.B.3.) As Dr. Westreich admitted, no “person emerging from the [Comer] study was less dependent on heroin than when they started.” (Westreich 188:13-16; *see also* PFOF ¶ 189.) The Comer paper’s conclusion was that “[f]uture studies” were needed to “evaluate the clinical utility” of the formulation for treatment, because that had not been determined. (Comer at .0015; PFOF ¶ 190.) Accordingly, Teva has not proven that, as of April 2004 and without hindsight, a POSA would have had a reasonable expectation of success of clinical utility based on the small sample size and study nature of the Comer paper, especially in light of the expressed observations about increased cravings.

BioTek’s own actions confirm this. The next BioTek publication, the Nuwayser patent, “has no information on the use of a naltrexone formulation other than the copy” of Figure 1 from the Comer paper. (Westreich 209:24-210:2.) In fact, Dr. Westreich went so far as to admit that he had “not cited *any* prior art publication reporting use of a BioTek formulation and achieving a reduction in opioid dependence.” (Westreich 204:9-12 (emphasis added).) And BioTek never advanced its formulation into Phase III clinical trials and never reached its development goal of “an injectable naltrexone product that can be prescribed to humans.” (Kerrigan (5/3/22) Tr. 55:4-7, 55:20-23; PFOF ¶¶ 98-99.)

Teva’s arguments are also self-contradictory. (PFOF ¶¶ 193-197.) Teva relied on the Leavitt paper, but that paper touted the FDA-approved oral naltrexone treatment of 50 mg/day, calling it “optimal.” (Leavitt at .0006.) The Comer paper discussed 50 mg/day as the “standard dose” used for clinical treatment. (Comer at .0014 (“Therefore, the amount of drug found in plasma after depot naltrexone administration is lower than the amount found after a standard dose of naltrexone used clinically for treating heroin dependence (50 mg/day).”).) Tice referred to using a formulation to achieve a “comparable” AUC to oral naltrexone. (Tice at 14:37-64, 15:57-61.) Teva failed to prove that a POSA would reasonably expect success for a treatment with a long-acting formulation that had a three-fold higher naltrexone exposure compared to the optimal dose of oral naltrexone. (PFOF ¶¶ 193-197; COL ¶ 290.)

A POSA would have understood from the Comer paper’s discussion of the low and high doses of the BioTek formulation that increasing exposure to naltrexone increased cravings for heroin. (*See supra* Argument § I.C.1.) And a POSA arriving at the claimed invention would also have had to give a single injection of more than 300 mg of naltrexone, disregarding concerns expressed in the prior art Kranzler paper regarding higher doses and injection volumes causing

more significant injection site reactions. (*See id.*) Again, a POSA without hindsight would not have had a reasonable expectation of success with a larger injection of naltrexone than that used in the Comer and Kranzler papers.

**D. Teva Did Not Prove by Clear and Convincing Evidence That Claim 13 Would Have Been Obvious Over Comer, Nuwayser, and Leavitt**

Dependent Claim 13 specifies a further component of the formulation used in the method of treatment, where the formulation must have about 35% by weight naltrexone. (PFOF § VI.C.) The evidence at trial established that the Comer paper did not describe the BioTek formulation used in the study, and Drs. Westreich and Yaman asserted that a POSA “would need the Nuwayser patent to effectively use Depotrex.” (Westreich 208:24-209:2; Yaman 329:1-10, 343:22-344:5; *see also* PFOF ¶¶ 155-156, 201.) The “sum total” of their opinion that Claim 13 would have been obvious, however, was a single sentence in Nuwayser that generally discusses a range of **0.1 to 80% or more** by weight of “an active ingredient.” (Westreich 211:22-212:12; *see also* PFOF ¶ 202.) As Dr. Westreich admitted, however, this discussion in Nuwayser was actually referring to “25 specific active ingredients” and “a general description of even more possible active ingredients.” (Westreich 213:16-214:15; *see also* PFOF ¶¶ 203-204.) The only examples of naltrexone formulations in the Nuwayser patent in fact directed a POSA “to use more than 50 [%]” naltrexone. (Westreich 216:4-8; *see also* PFOF ¶¶ 203-206.)

In other words, according to Teva’s own witnesses, the formulation used in the Comer paper would have been about “20 [%] higher than the 35 [%] number” required in Claim 13. (Westreich 215:15-17; *see also* PFOF ¶ 204.) Teva’s witnesses did not provide any motivation for a POSA to modify such a long-acting formulation with greater than 50% naltrexone to arrive at the claimed 35% naltrexone with a reasonable expectation of success (PFOF ¶¶ 205-206). *See, e.g., In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984) (“The mere fact that the prior art could be

so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification.”).

**E. Teva Did Not Prove by Clear and Convincing Evidence That Claim 10 Would Have Been Obvious Over Comer, Nuwayser, and Leavitt**

Claim 10 is focused exclusively on the *treatment of individuals afflicted with alcohol dependence* with a single injection of a long-acting formulation containing 310-480 mg of naltrexone in a PLGA polymer, which achieves three times greater naltrexone exposure compared to oral naltrexone. (PFOF § VI.D.) The Comer, Nuwayser, and Leavitt publications, however, do not involve administering long-acting naltrexone to individuals afflicted with alcohol dependence. (PFOF ¶¶ 208-209.) Comer excluded persons dependent on alcohol. (*See* Westreich 186:11-22 (“Comer did not administer naltrexone to individuals afflicted by alcohol dependency.”).)<sup>19</sup> When the Comer paper mentions long-acting naltrexone as being effective for alcohol, citing the Kranzler paper, “Comer is referring to a formulation containing 206 [mg] of naltrexone,” as Dr. Westreich admitted. (Westreich 187:21-188:5.) According to Dr. Westreich, the 1998 Kranzler paper reported that a single injection of 206 mg naltrexone “could be effective when administered every four weeks for alcohol dependence” (Westreich 181:12-14), though it also was reported to cause indurations (PFOF § IV.C.7).

The only publication in the prior art that used the BioTek formulation in an effort to treat alcohol-dependent patients was the Kranzler paper. (PFOF § IV.B, ¶¶ 208-210.) Teva’s witnesses, however, did not argue that Kranzler taught Claim 10. In fact, Teva could not make this argument

---

<sup>19</sup> Nuwayser does not discuss treating an individual who is afflicted with alcohol dependence. (PFOF § IV.C.9.) While Levitt does discuss treating an individual who is afflicted with alcohol dependence, its disclosures are limited to oral naltrexone. (PFOF § IV.C.10.)

because Kranzler, in discussing the single injection of 206 mg of naltrexone, suggested that the dose per injection should be *reduced*.

If, as Teva asserts, Kranzler showed 206 mg was safe and effective for treating alcohol dependence, a POSA would not have been motivated (without hindsight) to substantially increase the amount of naltrexone by at least 50% to the claimed range of about 310-480 mg naltrexone to treat individuals afflicted by alcohol dependence with a reasonable expectation of success.

Teva's lack of clear and convincing proof on Claim 10 lays bare its improper reliance on hindsight to try to recreate the invention in the prior art based on Alkermes's own work.

**F. Teva Did Not Prove by Clear and Convincing Evidence That Claim 2 Would Have Been Obvious Over Comer, Nuwayser, and Leavitt**

Teva also failed to prove obviousness of Claim 2, which incorporates the requirements of Claim 1 and requires that a patient be treated for alcohol or opioid dependence with a single injection of a long-acting naltrexone formulation containing 310-480 mg naltrexone and PLGA *once every four weeks, for 24 weeks*. (PFOF § VI.E.)

As Dr. Westreich admitted, "Comer did not repeat administrations over a period of time" (Westreich 190:10-12), and "none of the BioTek studies, in fact, involved giving the BioTek Depotrex formulation every month to individuals for a period of 24 weeks" (Westreich 190:14-19; *see also* PFOF ¶ 214). None of the prior art involved even one injection of a BioTek formulation containing more than 206 mg of naltrexone (*i.e.*, the amount given in Kranzler as a single injection). Without hindsight, a POSA would have had no information about efficacy, safety, or tolerability after repeated, monthly administrations of a single injection of a long-acting formulation containing 384 mg of naltrexone.

A POSA also would have learned from the Comer paper that two injections of 192 mg naltrexone resulted in higher cravings for heroin, making it implausible that a POSA, without

hindsight knowledge of Alkermes’s invention, would have found it obvious to treat patients addicted to heroin for 24 weeks with 384 mg of naltrexone. As Dr. Weiss explained, a formulation that results in high cravings would lead to relapse — not repeated use of that therapy for 24 weeks. (PFOF ¶ 215.)

Finally, a POSA would have believed that administering a single injection containing 384 mg naltrexone in the formulation would have caused indurations, which could last for as long as five weeks. (PFOF ¶ 216.) As Drs. Little and Weiss explained, such indurations would decrease tolerability and negatively affect patient compliance, which would have prohibited repeat administrations every four weeks for six months. (*See* Little 833:20-834:8 (“[I]f one were to do repeat administrations, that’s when I think you would really see the effects of the negative side effects that you see in the Kranzler article . . . compounded amount of the formulation being administered again and again at that local site.”); *see also* Weiss 553:16-24 (“[I]f nobody is going to take [the injection] a second time because they’ve got . . . this injection reaction, it’s not really gonna be an effective treatment.”).) There was no clear and convincing evidence that a POSA, without hindsight, would give repeated injections every month in amounts higher than those reported to cause indurations (or that a person with alcohol or opioid dependence would continue taking such a treatment).

**G. Objective Indicia of Nonobviousness Reinforce That Teva Failed to Establish Obviousness of the Asserted Claims by Clear and Convincing Evidence**

Teva failed to prove a motivation to modify the prior art to achieve the claimed invention with a reasonable expectation of success, which alone defeats its defenses. Nonetheless, objective indicia — which can further help to avoid hindsight bias, *Power Integrations, Inc. v. Fairchild Semiconductor Int’l, Inc.*, 711 F.3d 1348, 1368 (Fed. Cir. 2013) — confirm Teva’s failure to prove obviousness by clear and convincing evidence.

**Nexus:** Because the FDA-approved use of “Vivitrol is an embodiment of the ’499 Patent” (Yaman 397:17-19), and Teva stipulated that its proposed generic copy of Vivitrol<sup>®</sup> infringes, a “nexus” exists to the patented subject matter—*i.e.*, there is a relationship between the claimed subject matter of the patent and the particular objective indicia (PFOF § VII.A). *See, e.g., WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329-30 (Fed. Cir. 2016); *see also* COL § X.E.1.<sup>20</sup>

Teva’s expert, Dr. Yaman, opined that no nexus exists here because Medisorb<sup>®</sup> (Alkermes’s brand PLGA) was claimed in an earlier ’477 patent. (*See* Yaman 367:12-23.) But Medisorb<sup>®</sup> (and PLGA more generally) is an “inactive ingredient,” which by itself would provide no clinical benefit to patients. (PFOF § VII.A.) In contrast, the Asserted Claims are directed to a novel method of treating patients in need of naltrexone, and that combination of the claimed components of the ’499 Patent provides favorable outcomes for patients. (*See* Little 791:25-792:17, 835:1-837:16; *see also supra* Background § I.B.) As Dr. Yaman ***admitted***, the earlier ’477 patent does not even “disclose a long-acting naltrexone formulation.” (Yaman 426:5-11; *see also* PFOF § VII.A.) As such, Teva failed to rebut the presumption of nexus at trial.

**Long-felt But Unmet Need:** Since the early 1980s, there was a need for a new or improved treatment option for treating the chronic diseases of alcohol or opioid dependence that was safe, effective, and had sufficient tolerability so as to increase compliance compared to oral naltrexone. (PFOF ¶ § VII.B.) While others (including BioTek) attempted to develop a long-acting naltrexone

---

<sup>20</sup> Teva’s counsel spent time asking Dr. Little on cross-examination hypotheticals about a portion of the Vivitrol<sup>®</sup> label advising what to do if the needle should clog (*see* Little 911:14-917:19), but that line of questioning was irrelevant to any issue in the case. The ordinary use of Vivitrol<sup>®</sup>, according to the label, is a single monthly injection. (*See* Vivitrol<sup>®</sup> Label (2020) at .0001, .0003, .0022, .0024, 0026-27.) Alkermes is not relying on the occurrence of a clogged needle as an embodiment for objective indicia; it has nothing to do with deciding infringement, since Teva stipulated to infringement; and it is not intrinsic evidence relevant to claim construction. Finally, none of Teva’s experts discussed it in their opinions.

formulation, none other than Vivitrol® actually resulted in a treatment option. (PFOF §§ IV.B, VII.B-C.) Indeed, Vivitrol® met a need for a new or improved treatment option for alcohol or opioid dependence with improved compliance over oral naltrexone and remains the first and only long-acting injectable naltrexone formulation approved by the FDA (PFOF § VII.B). *See, e.g., Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009); *see also* COL § X.E.2.

**The Failure of Others:** As early as the 1980s, there were a handful of limited studies exploring a long-acting formulation of naltrexone, but none resulted in a successful treatment option for patients, *i.e.*, safe, effective, and with sufficient tolerability so as to increase compliance over daily naltrexone. (PFOF §§ IV.B, VII.C.) After decades without success, Vivitrol® became the first (and still only) long-acting naltrexone injection approved by the FDA (PFOF § VII.C). *See, e.g., In re Cyclobenzaprine*, 676 F.3d at 1082-83 (explaining that evidence of objective indicia is particularly probative when it demonstrates “both that a demand existed for the patented invention, and that others tried but failed to satisfy that demand.”); *see also* COL § X.E.3.

**Industry Skepticism:** As of April 2004, there was skepticism as to the ability to come up with a long-acting naltrexone treatment, including one that was safe and effective and induced greater compliance. (PFOF § VII.D.) As the evidence at trial showed, there was skepticism among clinicians — particularly those whose patients did poorly with oral naltrexone — reinforced by the New England Journal of Medicine publication in 2001 (Krystal) finding no evidence that oral naltrexone worked for alcohol dependence. (PFOF § VII.D.) Moreover, many patients preferred agonist-type treatments for opioid dependence, often not choosing or quickly quitting oral naltrexone and relapsing. (PFOF §§ IV.A, VII.D.) In fact, the skepticism surrounding oral naltrexone was so strong that, even after FDA approval of Vivitrol®, the medical community did

not immediately accept its utility. (PFOF § VII.D.) But as experience with Vivitrol® became more widespread, and its benefits were realized in practice, Vivitrol® was accepted by the medical field (PFOF § VII.D). *See, e.g., Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 885-86 (Fed. Cir. 1998) (skepticism of those in the art — even if such skepticism does not amount to evidence that the art taught away from the claimed invention — is “relevant and persuasive evidence of nonobviousness”); *see also* COL § X.E.4.

**Unexpected Properties:** In view of what was being reported about both oral and experimental long-acting formulations of naltrexone (*e.g.*, BioTek’s formulations) before Vivitrol®, such as issues with efficacy and tolerability (including injection site reactions), and side effects (such as increased cravings), a POSA would not have expected the claimed treatment method using a single injection of 310-480 mg of naltrexone in a long-acting formulation to achieve an AUC that is about three times higher than that achieved by 50 mg/day oral naltrexone, to be safe, effective, and tolerable (PFOF § VII.E). *See, e.g., Millennium Pharm.*, 862 F.3d at 1367-8 (“[I]nvention is not a matter of what the inventor intended when the experiment was performed . . . Unexpected results are shown in comparison to what was known, not what was unknown”); *see also* COL § X.E.5.

**Copying:** Teva argued that Comer and Nuwayser render obvious the ’499 Patent, but Teva is not seeking to market a product involving two injections of amounts of naltrexone smaller than that claimed every month, or seeking to do so by copying the Nuwayser patent formulation. (PFOF § VII.F.) Teva also is not seeking to simply sell oral naltrexone. (PFOF § VII.F.) Teva has made a decision to copy the invention of the ’499 Patent, *i.e.*, Vivitrol®, by filing its ANDA, recognizing the value of the invention despite the prior art Teva cites. (PFOF § VII.F.) That is a real world fact on this record that is consistent with nonobviousness. *See, e.g., Ortho-McNeil Pharm., Inc. v.*

*Mylan Labs.*, 348 F. Supp. 2d 713, 759 (N.D.W. Va. 2004) (“[T]he Court finds that [a generic drug manufacturer]’s decision to copy [one product] instead of [another] is significant evidence of non-obviousness.”); *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008) (evidence of copying is a “respected source[] of objective evidence of nonobviousness”); *see also* COL § X.E.6.

\* \* \*

For the reasons above, and in Sections VI and VII of Plaintiffs’ Proposed Findings of Fact, Teva failed to meet its burden of proving, by clear and convincing evidence and without hindsight, that the Asserted Claims would have been obvious to a POSA at the time of the invention.

## **II. Teva Did Not Prove By Clear and Convincing Evidence That the Comparative AUC Limitation Is Indefinite**

Teva presented two flawed arguments to support its claim that the comparative AUC limitation of Claim 1 is indefinite: that a POSA would not have understood (1) the AUC value of oral naltrexone, or (2) the time interval for calculating the AUC of a long acting naltrexone formulation. (PFOF ¶ 244.) But Teva failed to establish either argument by clear and convincing evidence because Dr. Yaman did not properly view the claims from the perspective of a POSA with an understanding of standard pharmacokinetic measurements. (PFOF § VIII; COL § X.F.)

The law requires only that the claims of the patent, when viewed in light of the specification and prosecution history, “inform those skilled in the art about the scope of the invention with reasonable certainty.” *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 910 (2014) (explaining that “reasonable certainty” does not require absolute or mathematical precision). “[A] claim is not indefinite if a person of skill in the art would know how to utilize a standard measurement method . . . to make the necessary measurement,” and “[a] patent need not explicitly include information that is already well known in the art.” *Presidio Components, Inc. v. Am. Tech.*

*Ceramics Corp.*, 875 F.3d 1369, 1376 (Fed. Cir. 2017) (citation omitted); *see also Sonix Tech. Co. v. Publ'ns Int'l, Ltd.*, 844 F.3d 1370, 1377-80 (Fed. Cir. 2017) (a claim term of degree is not indefinite if there is “an objective baseline through which to interpret the claims”).

**First**, a POSA reading Claim 1 would have understood that the AUC language was describing a comparison between the AUC of a long-acting naltrexone formulation and the AUC of 50 mg/day oral naltrexone. (PFOF § VIII.A.) At trial, the experts agreed that a POSA would have understood that such a comparison would be done using a comparative PK study, and that a POSA could design such a comparative PK study with reasonable clarity.<sup>21</sup> (PFOF ¶ 247.) Despite this agreement, at no point during trial did Teva’s witnesses attempt to apply the undisputed standards of a comparative PK study to its indefiniteness analysis.<sup>22</sup> Instead, Teva relied on Dr. Yaman’s conclusions based on a cross-study comparison, which is a “common pitfall” that a POSA would have avoided because they “are dangerous and can lead to false conclusions.” (PFOF ¶ 255.)<sup>23</sup>

**Second**, when conducting the comparative PK study for a formulation that is being used in a long-acting treatment method, a POSA would have used the treatment period between

---

<sup>21</sup> As the experts explained at trial, such comparative PK studies were routinely used in drug development programs. (PFOF ¶¶ 247-251, 254-255 n.34.) A POSA would also see that Dr. Ehrich used such a study submitted during prosecution of the '499 Patent, which further confirms the reasonable clarity for a POSA. (PFOF ¶¶ 252-253; COL ¶ 311.)

<sup>22</sup> Teva pointed to the phrase an “individual in need of naltrexone” in the claims to imply that the comparative PK study would be conducted in a single sick patient in need of naltrexone. Such an interpretation, however, is not what the claim says and is inconsistent with the intrinsic evidence that made clear that the claimed comparative AUC limitation is derived from a PK study using a group of healthy subjects (PFOF ¶¶ 252-253) — which is how a POSA understands how a comparative PK study is conducted (PFOF ¶¶ 250-251).

<sup>23</sup> Teva’s assertions about a “first pass effect” do not prevent a POSA from having reasonable certainty about the scope of Claim 1, and POSAs routinely deal with this phenomenon by using a comparative PK study. (PFOF ¶¶ 254-255.)

administrations when calculating the time interval for the AUC of a long acting naltrexone formulation. (PFOF § VIII.B.) This straightforward use of the treatment period to calculate the AUC would have been routine, and the Patent Office never had any issues with the comparative AUC limitation in this regard. (PFOF ¶ 260 n.38.) The patent specification and prosecution history make this clear to a POSA. (COL ¶ 311.) A POSA would have understood from the specification of the '499 Patent that a long-acting naltrexone formulation could treat a patient for a defined period before re-administration, such as for four weeks. (PFOF ¶¶ 257-258.) And the experts agreed at trial that a POSA would have been able to design a long-acting formulation to match that specified time period. (PFOF ¶ 258.) In other words, if the treatment period was every four weeks between administrations, then the formulator would design a formulation that would be administered every four weeks (*i.e.*, every 28 days).<sup>24</sup> (PFOF ¶¶ 258-261.) And the AUC would be calculated for that four-week treatment period.

Further, Teva's witnesses did not testify that Claim 2 was indefinite in this regard since Claim 2 is expressly limited to a treatment period of four weeks (*i.e.*, 28 days). (PFOF ¶ 262.)

### **III. Teva Failed to Prove by Clear and Convincing Evidence That the Asserted Claims Lack Written Description**

Teva argued that, if the limitation of Claim 1 "wherein the serum AUC of naltrexone is about three times greater than that achieved by 50 mg/day oral administration" was not obvious, it lacks written description in the alternative. (PFOF § IX.) As an initial matter, Teva blurred the well-established lines between the defenses of obviousness and written description. (COL § X.G.) There is a critical temporal difference. An obviousness analysis must exclude all hindsight knowledge of the invention and disclosures in the patent. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S.

---

<sup>24</sup> If the administration frequency was, instead, every three weeks or two weeks, the formulation would instead be designed for administration every three weeks or two weeks. (PFOF ¶ 258.)

398, 421 (2007); *Insite Vision*, 783 F.3d at 859-61. On the other hand, when considering whether a patent provides sufficient written description support, the ordinarily skilled artisan has full knowledge of the prior art ***and the teachings of the patent specification***. (COL § X.G.) A POSA who has read the claims and specification of the '499 Patent is given a wealth of information about the invention. (PFOF §§ III.A, IX.)

Dr. Yaman testified that the claims lack written description because “the claims only refer to a biocompatible polymer being PLGA” and the specification “didn’t give any other examples, other than [Medisorb®].” (Yaman 384:18-386:21.)

That testimony was inconsistent with the patent specification itself. As Dr. Little testified, a POSA would have understood that Medisorb® is simply the name of Alkermes’s brand PLGA, and that other companies sold similar PLGA polymers that formulators can use for similar purposes. (PFOF ¶ 265.) Examples of other suitable extended release technologies are specifically described in the specification of the '499 Patent, including Prolease® and Resomer®. (PFOF ¶¶ 52, 265.)

Teva’s experts agreed that the '499 Patent discloses a working example of a long-acting formulation that achieves the claimed AUC profile, which a POSA could reproduce. (PFOF ¶¶ 54, 269.) The '499 Patent specification discloses the preferred characteristics of these polymers for the claimed invention. (PFOF ¶¶ 52, 265.) Dr. Yaman also admitted that a POSA would have been able to make a long-acting formulation according to the '499 Patent, and would have found it routine to adjust that formulation as needed to achieve the claimed AUC. (PFOF ¶¶ 267-270.)

In sum, the '499 Patent adequately described the claimed inventions, and Teva failed to prove by clear and convincing evidence that the patent specification and claims do not “reasonably convey[] to [a POSA] that the inventor had possession of the claimed subject matter as of the filing

date.” *Vanda Pharms., Inc. v. West-Ward Pharms. Int’l Ltd.*, 887 F.3d 1117, 1136 (Fed. Cir. 2018); *see also* COL § X.G.

### **CONCLUSION AND REMEDY**

For the reasons set forth above, and in Plaintiffs’ Proposed Findings of Fact, Plaintiffs’ respectfully request that the Court find that Teva has failed to meet its burden of proving by clear and convincing evidence that the Asserted Claims are invalid.<sup>25</sup> As such, as discussed in more detail in Section X.H of Plaintiffs’ Conclusions of Law, Plaintiffs are entitled to an Order pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval of Teva’s ANDA No. 213195 be a date that is not earlier than the expiration of the ’499 Patent.

---

<sup>25</sup> To the extent Teva seeks to rely in its post-trial briefing on the PTAB’s preliminary decision to institute (*i.e.*, commence) an *inter partes* review proceeding, despite that (1) the underlying record of the PTAB decision was different and not admitted into evidence here, (2) the legal standards for an institution decision are different from the standards in a court proceeding, and (3) no Teva witness offered any testimony about this decision, Alkermes maintains the objections set forth in its February 18, 2023 Bench Memo (D.I. 207). The decision is not probative and should be given no weight.

Dated: April 12, 2023

*Of Counsel:*

Bruce M. Wexler  
Isaac S. Ashkenazi  
Max H. Yusem  
Lucas L. Kressel  
David Feigenbaum  
Sarah E. Spencer  
PAUL HASTINGS LLP  
200 Park Avenue  
New York, New York 10166

Respectfully submitted,

s/ Charles M. Lizza

Charles M. Lizza  
William C. Baton  
Sarah A. Sullivan  
SAUL EWING LLP  
One Riverfront Plaza, Suite 1520  
Newark, NJ 07102  
(973) 286-6700  
clizza@saul.com

*Attorneys for Plaintiffs  
Alkermes, Inc. and  
Alkermes Pharma Ireland Limited*